IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S) : Deborah C. Mash
SERIAL NO. : 09/486,613
FILED : February 29, 2000
FOR : Noribogaine in the Treatment of Pain and Drug Addiction
GROUP ART UNIT : 1617
Examiner : S.A. Jiang

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United States Patent and Trademark Office
P.O. Box 1450
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Declaration of Dr. Deborah C. Mash

S I R :

1. I, Deborah C. Mash, declare as follows:

2. I am a citizen of the United States of America.

3. I am the sole inventor of the subject matter of the above-referenced patent application.

4. I have over 20 years experience as a Ph.D. level researcher in the pharmaceutical/biological sciences.

5. I am presently a Full Professor in the Department of Professor of Neurology and Molecular and Cellular Pharmacology, University of Miami School of Medicine, Miami, Florida, and have held that position since June, 1997.

6. Since 1996, I have been the Jeanne C. Levey Professor of Parkinson's Disease Research at the Universitiy of Miami, Miami, Florida.

7. Since, 1995, I have been a Member, Scientific Advisory Panel, Heffter Research Institute, Lafayette, Indiana.

8. Since 2000, I have been a Member, Scientific Advisory Board for Life Extension, Fort Lauderdale, Florida.

9. From 2000-2003, I was a a Member, National Institutes of Health, Brain Disorders & Clinical Neuroscience ZRG1 (BDCN-6).

10. In 2001, I was a Member, National Institutes of Health, Center of Biologic Research and Excellence (COBRE).

11. In 2002, I was a Visiting Scholar, Departments of Psychology and Biology, Victoria University, Wellington, New Zealand.

12. From 1991-1996, I was a Member, National Institutes of Health, NINDS-NSPA Program Project Review Committee A.

13. From 1991-1997, I was Associate Professor of Neurology and Pharmacology, University of Miami School of Medicine, Miami, Florida.

14. Since 1990, I have been Associate Director for Basic Research, Comprehensive Drug Research Center.

15. From 1986-1991, I was Assistant Professor of Neurology and Pharmacology, University of Miami School of Medicine, Miami, Florida.

16. From 1984-1986, I was a Postdoctoral Fellow in Neurology (Neuroanatomy), Harvard Medical School, Boston, Massachussetts where I conducted human and primate

architectonic studies of cholinergic receptor subtypes under the direction of M-Marcel Mesulam, M.D.

17. From 1980-1984, I was a graduate student in pharmacology, University of Miami School of Medicine, Miami, Florida where my research was in biochemical and autoradiographic studies of muscarnic receptor subtypes in rat and human brain. In 1984, I received my Ph.D. in Pharmacology (Neuropharmacology) from the University of Miami School of Medicine, Miami, Florida. My dissertation was "Autoradiographic localization of M_2 muscarine receptors in the rat brain suggests a presynaptic location on cholinergic tracts: Implications for Alzheimer's disease".

18. In 1980, I received a M.S. degree in Pharmacology and Toxicology (Neuropharmacology) from the Florida A & M University, Tallahassee, Florida.

19. In 1975, I received a B.A degree (Cum Laude) in Experimental Psychology from Florida State University, Tallahassee, Florida.

20. My primary areas of technical expertise include the following:

- Neuropharmacology, especially brain neuropharmacology;
- Neurodegenerative disorders;
- Addictive disorders/addiction; and
- Opioid Pharmacology.

21. I have published over one hundred eighty (180) peer-reviewed articles, a number of which relate to ibogaine and neuribogaine, their pharmacological effects and metabolism of ibogaine to neuribogaine.

22. I have received numerous honors and awards including:

1980-84	NIH Predoctoral Traineeship
1984-86	NIH Postdoctoral Traineeship
1984	Upjohn Award. First Place Graduate Student Category

1984	Roche Laboratories Award in Clinical Sciences
1984	James E. Beale II Aware in Neuroscience
1984	Boehringer Ingelheim Research Award
1996	Jeanne C. Levey Professor Neurology, Endowed Chair
2002	Professional Leadership Award, National Parkinson's Foundation
2002	Alzheimer's Associate Medical Honoree

23. I am a member of numerous professional and honorary organizations including the Society for Neuroscience, Sigma Xi, International Brain Research Organization, American Association, New York Academy of Sciences, American Academy of Neurology and the American Society for Pharmacology and Experimental Therapeutics.

24. I am or have been an *ad hoc reviewer* of articles in a number of scientific publications including Brain Research; Neurology; Journal of Neurochemistry; Neurobiology of Aging; Journal of Immunopharmacology; Journal of Neuroscience, Pharmacology and Behavior; Life Sciences (Pharmacology Letters); European Journal of Pharmacology; Annals of Neurology; Neurology; Journal of Comparative Neurology; Synapse; Psychopharmacology; and the American College of Neuropsychopharmacology.

25. I am sole inventor of the subject matter of patent application number serial number 09/486,613, entitled "Noribogaine in the Treatment of Pain and Drug Addiction". I am familiar with the subject matter presently claimed which is directed to the use of noribogaine as an opioid agonist (μ receptor agonist) in the treatment of pain as claimed. I understand that my invention as set forth claims 6-9 and 25-30 of the response submitted with this declaration are directed to methods of treating pain in a patient with an opioid receptor agonist without addiction to the patient, the method comprising administering to the patient a pharmaceutical composition which consists essentially of an amount of noribogaine or its pharmaceutically acceptable salt to reduce or eliminate pain in the patient (claims 25-30), or alternatively noribogaine in combination with an opioid antagonist to reduce or eliminate pain in the patient (claims 6-9).

26. I have read the Examiner's office action dated September 26, 2005 and understand that the Examiner, on pages 3-10, essentially has rejected the present invention by suggesting that my invention does not indicate the *type* of pain which is treated, and that the references cited against my invention, namely Olney, U.S. patent no. 5,925,634 ("Olney") teaches my invention alone or that my invention is obvious over the teachings of Olney combined with other references, namely GB 841,697 ("GB"697") in view of Hussain, U.S. patent no. 4,464,378 ("Hussain"). I respectfully disagree.

27. The present invention as claimed is directed to a method of treating pain with noribogaine, which is an opioid agonist. Thus, using noribogaine, a patient may be treated with an opioid agonist without the addiction normally associated with the administration of a traditional opioid agonist such as morphine. This was unexpected. I understand that the Examiner contends that the claims do not teach which *type* of pain is treated with noribogaine, but the activity of noribogaine is as an opioid agonist in the treatment of pain. Contrary to the Examiner's contention, opioid agonists in the first instance are primarily useful for treating nociceptive pain, i.e., pain which is mediated primarily through the μ receptor. Nociceptive pain is distinguishable from neuropathic pain, which is mediated through NMDA receptors. Thus, by using the term "opioid agonist" in the claims, it is understood that noribogaine can used in the same manner that morphine (and other opioid agonists) can be used, but without the corresponding addiction which occurs with opioid use.

28. I am familiar with the reference Olney and I do not believe that Olney teaches my invention. In the first instance, to the extent that Olney teaches the use of ibogaine for pain (a proposition which is, in the first instance, questionable, given the psychotropic or hallucinogenic side effects of ibogaine), that use is for *neuropathic pain mediated through NMDA receptors*, not nociceptive pain mediated through μ receptors as in the case of noribogaine. It is noted here that even Olney indicates that ibogaine is used for neuropathic pain, *i.e. pain which does not respond conventionally to opiate drugs such as morphine* (see Olney abstract and column 7, lines 17-19). That neuropathic pain does not conventionally respond to opiate drugs and was generally known in the art as failing to respond to opiod drugs is also supported by the following references:

Hanks, *British Medical Bulletin,* 47, 3, 718-731 (1991); Kupers, et al., *Pain*, 47, 5-12 (1991); Cherny, et al., *Neurology,* 44, 857 (May, 1994); Martin and Hagan, *Journal of Pain Symptoms Management*, 14, 2, 99-117, (1997); Garcia and Altman, *Seminars in Arthritis and Rheumatism,* 27, 1, 1-16 (August, 1997); and Abstract, Shir, et al., *Harefuah,* 118, 8, 452-454 (1990), copies enclosed. It is noted that the art failed to recognize that ibogaine could be used to treat nociceptive pain (i.e., pain which can be treated with an opioid agonist) and obviously Olney does not teach such a method. Rather, Olney *at best* teaches that ibogaine may be used in certain circumstances to treat neuropathic pain which does not respond to an opioid agonist, because such neuropathic pain is mediated through a receptor (NMDA), upon which the opioid agonists were understood to be inactive. Thus, if Olney teaches anything, it is that ibogaine may be used to treat pain which does not conventionally respond to morphine and other opioid agonists, i.e., neuropathic pain which is mediated through NMDA receptors.

29. That ibogaine cannot be used to treat nociceptive pain in the same manner as morphine or noribogaine may be found in the present application in the examples on page 9-10. That example teaches that morphine and noribogaine are full μ-opioid receptor agonists (anti-nocicipetive agents), whereas ibogaine was essentially inactive in the assay (page 9). Thus, the experiment which is presented in the present application evidences that noribogaine is a full μ-opioid receptor agonist and has efficacy as an antinociceptive agent (page 9, line 21), whereas ibogaine clearly was not active and is not an antinociceptive agent. This experiment is consistent with the general understanding in the art that ibogaine does not exhibit μ-opioid receptor agonist activity and therefore, cannot be used as a substitute for morphine to treat nociceptive pain. From these experiments and a review of the art, a scientist would conclude that ibogaine is not useful for treating pain which responds to morphine (nociceptive pain).

30. Thus, ibogaine would not be used to treat nociceptive pain as a substitute for morphine because ibogaine does not have the type of activity (i.e., μ receptor agonist activity) consistent with the treatment of nociceptive pain. Prior to the present invention it was not known that noribogaine possessed μ receptor agonist activity and could be used as a substitute for morphine. Not only does noribogaine possess good antinociceptive (pain) activity, noribogaine

can be administered without the patient suffering from the withdrawal symptoms associated with morphine administration. This is clearly not taught by Olney. In fact, Olney teaches that the action of ibogaine and morphine are completely distinguishable because they treat different types of pain. The same is true for ibogaine and noribogaine.

31. When a patient is being treated for pain, the first agents which are used to treat pain are the antinociceptive opioid agonists. It is only after the opioid agonists are shown to be incompletely effective or ineffective that neuropathic pain is suspected and other agents are then used. Thus, in the first instance, ibogaine will never be used to treat nociceptive pain, based upon the teachings of Olney. Moreover, the experiment presented in the specification on pages 9-10 of the present application confirms Olney's teachings in this regard. Thus, pursuant to the teachings of Olney, Ibogaine may be used *alone* to treat neuropathic pain or in instances where the opioid agonists are incompletely effective, ibogaine may be combined with an opioid agonist to treat pain which has both antinociceptive and neuropathic attributes. But such a combination would only theoretically be used after initial use by the preferred agent, morphine. Thus, while the prior art anticipates the *possibility* of using ibogaine alone to treat neuropathic pain or ibogaine in combination with a traditional opioid agonist to treat pain having both neuropathic and nociceptive components, in practice opioids will invariably be used as the first step in the treatment of pain. Nonetheless, the present invention clearly distinguishes over both of these methods. Indeed, the Hanks, reference, *ibid.* at page 719, lines 9-12 of third full paragraph, presupposes that opioid therapy will *invariably be part of the therapeutic regimen* in treating pain of mixed origin.

32. As a separate note it is acknowledged that ibogaine metabolizes to noribogaine, as well as other metabolites. However, the pharmacokinetics of this metabolism and the concentration or amount of noribogaine which will accumulate in a patient will vary widely depending on the patient's genetics and other drugs a patient may be taking. The level of activity and/or the amount of one or more isoforms of cytochrome P450 present in the patient is reflective of the patient's genetics and about 5-10% or more of all patients may be characterized as poor metabolizers of ibogaine. In addition, other drugs/agents which a patient takes can

greatly influence the metabolism of ibogaine to noribogaine. In many instances, depending on the patient, that patient may be a poor metabolizer of ibogaine, or alternatively, other drugs the patient may be taking may substantially inhibit or influence the amount of noribogaine which will be produced from ibogaine during metabolism such that the amount of noribogaine is not always constant, known or substantial. Thus, even in the unlikely event that ibogaine was administered for treating neuropathic pain *alone*, such administration would not necessarily produce sufficient quantities of noribogaine to treat nociceptive pain, especially if that patient were a poor metabolizer or were taking other agents for the treatment of pain or other ailments. See, for example, Obach, et al., *Drug Metabol. Disp.*, 26, 8, 764-768 (1998) and Mash, et al., "Ibogaine in the treatment of heroin withdrawal." In: Ibogaine: Proceedings of the first International Conference., Alkaloid Series, Volume 56. Editors: Dr. K. Alper and Dr. S. Glick. Academic Press, San Diego, California pp 156-170, 2001, enclosed.

33. I further declare that all statements made herein of my own personal knowledge are rue and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and thc like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 12/21/05 _____

Deborah C. Mash